

Management of chemotherapy dose intensity for metastatic colorectal cancer (Review)

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Abstract. Chemotherapy dose intensity is a momentous parameter of antitumor clinical medication. In certain clinical trials, the actual application dose of the chemotherapeutic drugs is frequently different from the prescribed dose. The chemotherapy dose intensity completed in different trials is also variable, which has an impact on the treatment efficacy, disease prognosis and patient safety. When these agents are tested in the population, chemotherapy reduction and delay or failure to complete the planned cycle constantly occur due to age, performance status, adverse reactions and other reasons, resulting in the modification of the chemotherapy dose intensity. The present review analyzed the correlation between the chemotherapy dose intensity and the incidence of adverse reactions, the treatment efficacy and disease prognosis in clinical trials of metastatic colorectal cancer. Moreover, the clinical applications of chemotherapy dose intensity were discussed. Based on individual differences, the present review analyzed the clinical trials that examined the efficacy of the chemotherapy dose intensity in different patient populations. The conclusions suggested that different populations require a specific dose intensity to reduce treatment toxicity without affecting the curative effect.

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1. Introduction

Colorectal cancer is a highly prevalent digestive tract malignancy with the third highest incidence and the second highest mortality worldwide in cancer according to global cancer statistics in 2018 (1). The current major therapeutic modalities include surgery, chemotherapy, targeted therapy, radiotherapy and immunotherapy (2). The majority of the patients with metastatic colorectal cancer (mCRC) lose the opportunity of resection surgery at the initial diagnosis, while several problems have been encountered in the selection of the treatment population and the course of disease in radiotherapy, targeted therapy and immunotherapy (3,4). For example, radiotherapy is used in some patients with rectal cancer, and targeted therapy is used in patients with potential targets, such as cetuximab in RAS/BRAF wild-type patients. PD-1 monoclonal antibody can be used for patients with MSI-H or dMMR in first-line therapy. Chemotherapy is the main treatment for patients with mCRC due to its broad applicability (4). Patients with advanced malignant tumors experience complications with advanced age, cardiovascular and cerebrovascular diseases, abnormal liver and kidney function and tumor progression (5). In clinical practice, the dose of chemotherapeutic drugs is adjusted according to the actual situation as described above (for example, age or cardiovascular diseases), resulting in the occurrence of dose reduction, delay of the set cycle and adjustment of the chemotherapeutic regimen, which render the clinical medication incapable to match the standard scheme and dose of the guidelines (6).

The two most important variables in the regulation of the efficacy of the antitumor chemotherapeutic drugs are the adjustments of their combination and dose, which involve multiple dose-related concepts, as seen below (7). It has been reported that the dose intensity (DI) of chemotherapy can be further altered by adjusting the time interval of administration or the dosage (8,9). The DI of chemotherapy refers to the dose of chemotherapeutic drugs received by the patients per unit time. It is independent from the route of administration and is calculated by the dose of chemotherapeutic drugs received per square meter of body surface every week (7). The average relative DI (ARDI) refers to the average value of the actual DI of each chemotherapeutic drug, which is calculated as a percentage of the standard DI in the combined chemotherapy regimen (10,11). Pharmacodynamic evaluation involves the

estimation of the dose-effect curve and suggests that the higher the effective drug dose, the higher the improvement in the antitumor effect and the stronger the toxicity (12,13). It is important to address the influence of the change of the chemotherapy DI on the curative effect and disease prognosis. It remains unknown whether the reduction of the DI of chemotherapy can reduce drug efficacy and disease prognosis (14-16). In clinical practice, numerous factors affect the DI of chemotherapy and then affect the overall efficacy, prognosis and safety. By examining multiple clinical trials of mCRC, the present review analyzed the variations of chemotherapy DI in clinical trials and discussed the relationship between chemotherapy DI and treatment efficacy, disease prognosis and incidence of adverse reactions (Fig. 1).

2. Three-drug combination chemotherapy regimens

FOLFOXIRI is a combination of three core cytotoxic drugs: 5-fluorouracil (5-FU)/folinic acid, oxaliplatin (L-OHP) and irinotecan (CPT-11) (17). The FOLFOXIRI regimen has a relatively high DI. Based on the present medical guidelines, the Chinese Society of Clinical Oncology guidelines incorporated FOLFOXIRI into a first-level recommended regimen for patients with potentially resectable mCRC who are suitable for intensive treatment and are positive for RAS/BRAF mutations (18). The National Comprehensive Cancer Network (NCCN) guidelines recommend this regimen for patients with higher performance status scores (19). The Japanese Society for Cancer of the Colon and Rectum guidelines and the European Society for Medical Oncology guidelines recommend this regimen for patients who are suitable for high-intensity first-line chemotherapy (20,21).

The results of the Gruppo Oncologico Nord Ovest (GONO) phase III clinical trial in 2007 and the Hellenic Oncology Research Group (HORG) phase III clinical trial in 2006 enabled the development of the FOLFOXIRI protocol, which was included in the NCCN colon cancer guidelines (17,22). Both clinical trials explored the efficacy and safety of the FOLFOXIRI regimen in the first-line treatment of mCRC and employed the mature 5-FU, folinic acid and CPT-11 (FOLFIRI, a two-drug combination chemotherapy) regimen as the control. The preset doses of the three chemotherapeutic drugs in the GONO clinical trial were higher than those of the HORG clinical trial. Nevertheless, the former trial indicated a lower dose than the latter one in terms of final ARDI data, as summarized in Table I. In both trials, it was found that the incidence of chemotherapy delay and the reduction of the three-drug regimen was more significant than that of the two-drug regimen ($P < 0.05$). Regarding efficacy, the GONO trial indicated significant improvements in the following endpoints: Objective response rate (ORR), margin-negative resection rate of liver metastasis, progression-free survival (PFS) and overall survival (OS; $P < 0.05$). No significant differences were noted in the HORG trial. It is considered that the latter outcome is interrelated to the age of the enrolled subjects, their poor performance status and the low preset chemotherapy dose. In addition, the incidence of adverse events in the three-drug regimen group was significantly increased in both trials ($P < 0.01$).

The GONO and HORG data indicated that the three-drug regimen had a high clinical efficacy. However, the prospect of

combining chemotherapeutic with antiangiogenic drugs requires further investigation to evaluate the changes in ARDI, treatment efficacy, prognosis and safety. Angiogenesis is crucial to the development and progression of cancer and its inhibitory effect has been shown to be beneficial in patients with several different malignancies (23). Bevacizumab (Bev) has been shown to be beneficial to the survival of patients with mCRC in the following trials (24): TRIBE (25,26), TRIBE2 (27), OLIVIA (28) and STEAM trials (29). The TRIBE trial was a multicenter randomized phase III clinical trial conducted by the Italian GONO cooperation group, which mainly studied the efficacy and safety of the FOLFOXIRI three-drug regimen combined with Bev. This trial used FOLFIRI combined with Bev as the control group. The OLIVIA clinical trial was jointly carried out by 16 centers in Austria, France, Spain and the UK and mainly assessed the influence of the three-drug regimen combined with Bev on the resection rate of liver metastasis. Modified 5-FU/folinic acid and L-OHP (mFOLFOX-6) combined with Bev was used as the control group. The STEAM trial examined the efficacy of 5-FU/folinic acid plus L-OHP (FOLFOX) combined with Bev as the control group and mainly studied the feasibility of the three-drug regimen combined with the Bev synchronous regimen (continuous administration of three drugs combined with Bev for eight cycles) or the sequential regimen (FOLFOX or FOLFIRI combined with Bev alternating every two cycles). This was based on the consideration of the sequential selection of the treatment regimen and on the assessment of whether the American patient population could benefit from the three-drug regimen. The TRIBE2 trial was based on the satisfactory results of the TRIBE trial and focused on the sequential selection of specific treatment schemes. Moreover, this trial studied the feasibility of re-applying the FOLFOXIRI/Bev regimen following disease progression. This application of the FOLFIRI/Bev regimen, which was performed after the progression of the mFOLFOX-6/Bev regimen, was considered as the control group.

The aforementioned four clinical trials reported that the ARDI of the chemotherapy was decreased to a higher extent following the addition of Bev with that of the standard regimen, as summarized in Table II. The incidence of reduction and delay of the three-drug regimen combined with Bev was more significant than that of the two-drug regimen combined with Bev ($P < 0.001$). The TRIBE2 trial demonstrated that the ARDI of the second-line treatment was lower than that of the first-line treatment. Furthermore, the ARDI of the three-drug regimen combined with Bev was decreased by 7% and that of the two-drug regimen combined with Bev was decreased by 6%. Regarding the assessment of efficacy, the results indicated that the three-drug or two-drug chemotherapy regimens combined with Bev displayed improved efficacy and prognosis compared with those noted in the chemotherapy alone group. Moreover, it was shown that OS, PFS and ORR were improved. The incidence of adverse reactions, such as neutropenia, was approximately the same as that noted in the HORG and GONO trials. It should be noted that the addition of Bev increased the incidence of adverse reactions related to antiangiogenic targeted drugs, such as hypertension.

Following analysis of several classic clinical trials that included three-drug regimens, it was found that the DI of the three-drug regimen was higher than that of the two-drug

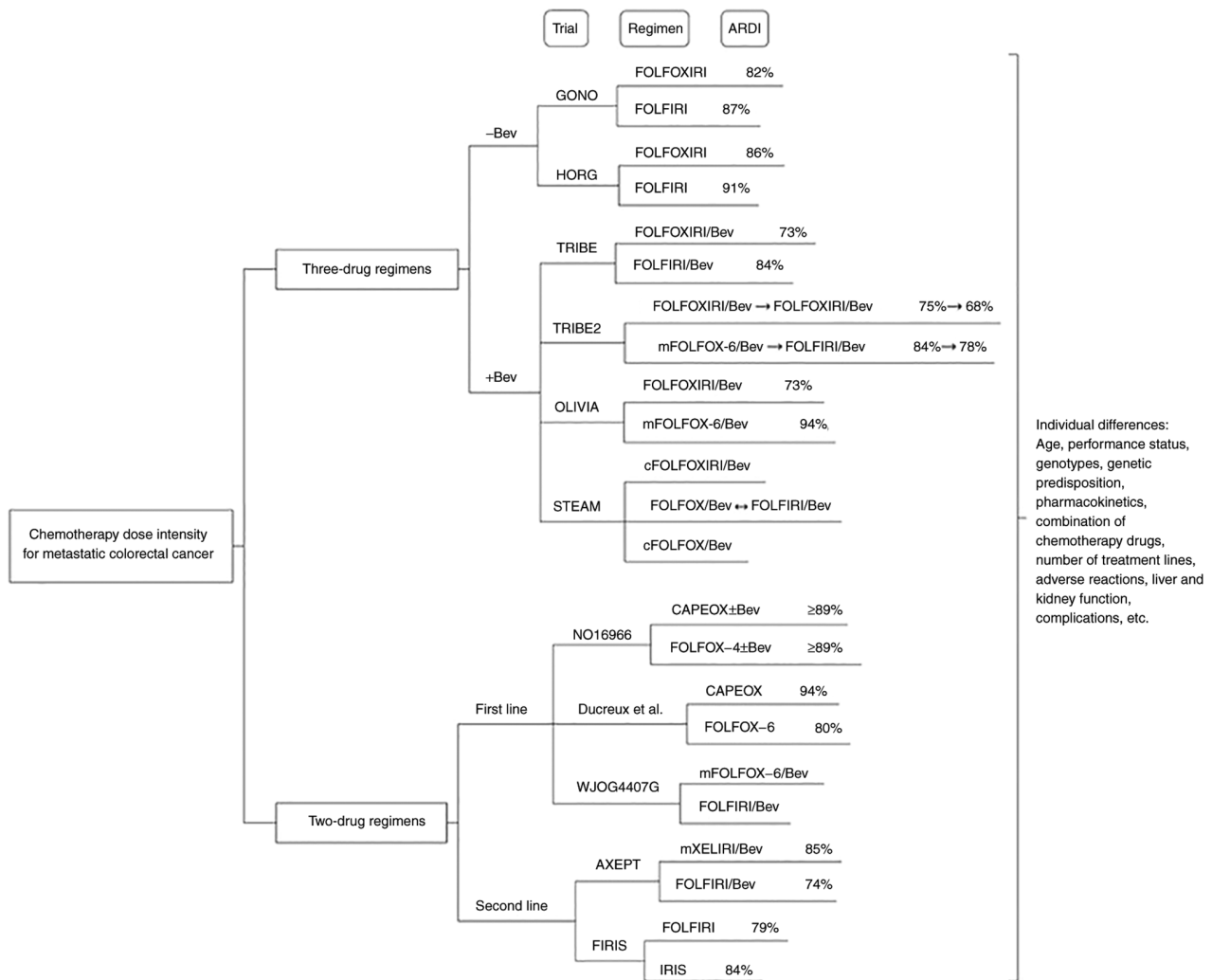


Figure 1. Flow chart of chemotherapy dose intensity in colorectal cancer clinical trials. ARDI, average relative dose intensity; Bev, Bevacizumab; cFOLF-
OXIRI/Bev, concurrently FOLFOXIRI/Bev; cFOLFOX/Bev, concurrently FOLFOX/Bev; FOLFOXIRI, 5-fluorouracil/folinic acid, oxaliplatin and irinotecan;
FOLFOX, 5-fluorouracil/folinic acid and oxaliplatin; FOLFIRI, 5-fluorouracil/folinic acid and irinotecan; CAPEOX, capecitabine and oxaliplatin; mXELIRI,
irinotecan and capecitabine; IRIS, S-1 and irinotecan.

regimen, whereas the actual DI of chemotherapy would descend due to patient tolerance and other problems encountered in the clinical environment (25-29). Subsequently, the DI was decreased following the combination with Bev. The increase in the number of drugs indicated improved benefits in efficacy and prognosis. However, considerable emphasis should be paid to the increase of the number of adverse reactions. The ARDI of the first-line treatment with the two-drug regimen could reach 83-94%, whereas that of the three-drug regimen could be maintained at 73-85% and that of the second-line treatment could be reduced by 5-7% (25-29). The actual DI of the chemotherapy is far more likely to decline in the subsequent line of treatment and that of the three-drug regimen is higher than that of the two-drug regimen. The tumor load of colorectal cancer and metastases in patients with advanced primary unresectable tumors is an important factor affecting survival (30). A significant correlation has been noted between ORR and the resection rate (30). The three-drug regimen can significantly improve ORR and increase the resection rate of metastatic lesions, which has important clinical value in reducing metastatic lesions and promoting secondary resection.

3. Two-drug combination chemotherapy regimens

The first-line two-drug regimen of mCRC, which is commonly used, includes FOLFOX, capecitabine (Cap) plus L-OHP (CAPEOX) and FOLFIRI. FOLFOX-4, FOLFOX-6 and mFOLFOX-6 are different in dosage and time, and both belong to FOLFOX. The two-drug regimen selects the combination of core cytotoxic drugs for the treatment of mCRC. The NO16966 trial compared CAPEOX and FOLFOX-4 and Ducreux *et al* compared CAPEOX and FOLFOX-6 (31-33). The preset dosage of L-OHP in FOLFOX-4, CAPEOX and FOLFOX-6 was 85 mg/m² q14d (once every 14 days), 130 mg/m² q21d (once every 21 days) and 100 mg/m² q14d, respectively, whereas the DI of L-OHP increased in FOLFOX-4, CAPEOX and FOLFOX-6. The DI of 5-FU in FOLFOX-6 was higher than that in FOLFOX-4. Based on the final ARDI data of the two trials, the actual DI of the FOLFOX-6 group was the lowest and was estimated to be only 80%, as shown in Table III. The comparison of the survival data of the simple chemotherapy group (group without Bev) of the two trials indicated that OS represented a gradually increasing trend in the FOLFOX-4,

Table I. Clinical trials of the three-drug regimens.

Clinical trial	Regimen	Average relative dose intensity, %	Dose intensity-related events, n	P-value	Overall survival, months	P-value	Progression-free survival, months	P-value	Other indicators, %	P-value	Grade 3 to 4 adverse events, %	P-value
Gruppo Oncologico Nord Ovest (17)	FOLFOXIRI	82%	Treatment cycles, 11	<0.05	22.6	<0.05	9.8	<0.05	ORR, 60%; R0 resection of liver metastasis, 36%	<0.05	Neutropenia, 50%	<0.05
	FOLFIRI	87%	Treatment cycles, 10		16.7		6.9		ORR, 34%; R0 resection of liver metastasis, 12%		Neutropenia, 28%	
Hellenic Oncology Research Group (22)	FOLFOXIRI	86%	Cycles delayed, 166; decrement cycles, 87	N/A	21.5	>0.05	8.4	>0.05	ORR, 43%	>0.05	Alopecia, 32%; diarrhea, 28%; neurotoxicity, 6%	<0.05
	FOLFIRI	91%	Cycles delayed, 101; decrement cycles, 40		19.5		6.9		ORR, 34%		Alopecia, 12%; diarrhea, 11%; neurotoxicity, 0%	

ORR, objective response rate; FOLFOXIRI, 5-fluorouracil/folinic acid, oxaliplatin and irinotecan; FOLFIRI, 5-fluorouracil/folinic acid and irinotecan.

Clinical trial	Regimen	Average relative dose intensity, %	Dose intensity-related events, % or n	Overall survival		Progression-free survival		Other indicators, %	Grade 3 to 4 adverse events, %	P-value
				months	P-value	months	P-value			
TRIBE2 (25,26)	FOLFOXIRI/Bev	73%	Incidence of delay, 16%; incidence of decrement, 21%	29.8	<0.05	12.1	<0.05	ORR, 65%	Neurotoxicity, 5%; stomatitis, 9% diarrhea, 19%; neutropenia, 50%	>0.05
	FOLFIRI/Bev	84%	Incidence of delay, 6%; incidence of decrement, 8%	25.8		9.7		ORR, 53%	Neurotoxicity, 0%; stomatitis, 4%; diarrhea, 11 %; neutropenia, 21%	
TRIBE2 (27)	FOLFOXIRI/Bev followed by FOLFOXIRI/Bev	First line, 75%; second line, 68%	Incidence of decrement, 58%	27.6	<0.05	19.2	<0.05	ORR, 62%; R0 resection of metastasis, 17%	Diarrhea, 17%; neutropenia, 50%; hypertension, 7%	<0.05
	mFOLFOX-6/Bev followed by FOLFIRI/Bev	First line, 84%; second line, 78%	Incidence of decrement, 47%	22.6		16.4		ORR, 50%; R0 resection of metastasis, 12%	Diarrhea, 5%; neutropenia, 21%; hypertension, 10%	
OLIVIA (28)	FOLFOXIRI/Bev	73%	Cycles to reach the indication of resection, 6	N/A	N/A	18.6	N/A	ORR, 81%; R0 resection of liver metastasis, 49%	Neutropenia, 50%; diarrhea, 30%	N/A
	mFOLFOX-6/Bev	94 %	Cycles to reach the indication of resection, 7	N/A		11.5		ORR, 62%; R0 resection of liver metastasis, 23%	Neutropenia, 35%; diarrhea, 14%	
STEAM (29)	Concurrently FOLFOXIRI/Bev	N/A	Complete eight cycles of treatment, 77%; treatment cycles, 8	N/A	>0.05	11.9	<0.05	ORR, 72%; R0 resection of liver metastasis, 16%	Neutropenia, 57%; hypertension, 22%; diarrhea, 22%	>0.05

Table II. Continued.

Clinical trial	Regimen	Average relative dose intensity, %	Dose intensity-related events, % or n	P-value	Overall survival, months	P-value	Progression-free survival, months	P-value	Other indicators, %	P-value	Grade 3 to 4 adverse events, %	P-value
	Sequentially FOLFOX/Bev	N/A	Complete eight cycles of treatment, 80%; treatment cycles, 9		N/A		11.4		ORR, 73%; R0 resection of liver metastasis,		Neutropenia, 41%; hypertension, 22%; diarrhea, 10%	
	FOLFIRI/Bev											
	FOLFOX/Bev	N/A	Complete eight cycles of treatment, 76%; treatment cycles, 8		N/A		9.5		ORR, 62%; R0 resection of liver metastasis, 6%		Neutropenia, 36%; hypertension, 16%; diarrhea, 12%	

Bev, bevacizumab; ORR, objective response rate; FOLFOXIRI, 5-fluorouracil/folinic acid, oxaliplatin and irinotecan; FOLFIRI, 5-fluorouracil/folinic acid and irinotecan; FOLFOX, 5-fluorouracil and oxaliplatin; mFOLFOX, modified 5-fluorouracil/folinic acid and oxaliplatin.

Table III. Clinical trials of first-line two-drug regimens.

Clinical trial	Regimen	Average relative dose intensity, %	Dose intensity- related events, n	P-value	Overall survival, months	P-value	Progression- free survival, months	P-value	Other indicators, %	P-value	Grade 3 to 4 adverse events, %	P-value
NO16966 (31,32)	CAPEOX ± Bev	≥89%	Treatment cycles, 12	N/A	-Bev, 18.8; +Bev, 21.6	N/A	-Bev, 7.3; +Bev, 9.3	N/A	ORR, 47%	N/A	Neutropenia, 7%; neurotoxicity, 6%; diarrhea, 19%	N/A
	FOLFOX-4 ± Bev	≥89%	Treatment cycles, 8		-Bev, 17.7; +Bev, 21		-Bev, 7.7; +Bev, 9.3		ORR, 48%		Neutropenia, 44%; neurotoxicity, 1%; diarrhea, 11%	
Ducreux <i>et al</i> 2011 (33)	CAPEOX	94%	Treatment cycles, 8	N/A	19.9	N/A	8.8	N/A	ORR, 42%	N/A	Thrombocytopenia, 12%; diarrhea, 14%; neurotoxicity, 11%; neutropenia, 5%	N/A
	FOLFOX-6	80%	Treatment cycles, 11		20.5		9.3		ORR, 46%		Thrombocytopenia, 5%; diarrhea, 7%; neurotoxicity, 26%; neutropenia, 47%	
WJOG4407G (39)	mFOLFOX-6/ Bev	N/A	Treatment cycles, 12.5	N/A	30.1	>0.05	10.7	<0.05	ORR, 62%	>0.05	Neutropenia, 35%; leukopenia, 5%; neurotoxicity, 22%	<0.05
	FOLFIRI/Bev	N/A	Treatment cycles, 15		31.4		12.1		ORR, 64%		Neutropenia, 45%; leukopenia, 11%; neurotoxicity, 0%	

Bev, bevacizumab; ORR, objective response rate; FOLFOX, 5-fluorouracil and oxaliplatin; mFOLFOX, modified 5-fluorouracil/folinic acid and oxaliplatin; CAPEOX, capecitabine and oxaliplatin.

CAPEOX and FOLFOX-6 groups. However, the difference was not statistically significant. From this evidence, it can be deduced that the slight change of the chemotherapy DI exhibited no significant impact on the overall patient survival. In the NO16966 trial, the survival benefit of the chemotherapy plus Bev was higher than that of the chemotherapy alone, which was consistent with the aforementioned conclusion. In the FOLFOX-6 group, the patients received a longer treatment duration, higher cumulative dose of L-OHP and demonstrated significant neurotoxicity, which led to the decrease of ARDI and the adjustment of the regimen in the subsequent stage of the treatment. The incidence of neurotoxicity was low when the FOLFOX-4 regimen was used with low DI. Based on the occurrence of adverse reactions, the FOLFOX-6 regimen was further modified and optimized to form mFOLFOX-6 regimen with a reduction in the dose of L-OHP from 100 mg/m² q14d to 85 mg/m² q14d. This facilitated the application of the mFOLFOX-6 regimen (34).

A meta-analysis aiming to compare CAPEOX and FOLFOX included six randomized controlled trials. Although the dose and infusion mode of the FOLFOX evolution regimens were different in the six trials, no significant difference was noted between PFS and OS (35). The difference noted in the FOLFOX evolution regimens was mainly interrelated to the incidence of adverse reactions, suggesting that researchers and clinicians should seek the lowest point of DI and adverse reactions on the premise of maintaining survival benefits. CAPEOX and FOLFOX have shown approximate efficacy in multiple large clinical trials and improved benefits were demonstrated in combination with Bev (35,36). The two regimens are a combination of 5-FU and L-OHP and the difference is mainly reflected in the incidence of adverse reactions. The CAPEOX regimen exhibits significant gastrointestinal toxicity and the FOLFOX regimen exhibits significant myelosuppressive toxicity. The advantage of the CAPEOX regimen lies in the convenience brought by oral chemotherapy drugs and the reduction of medical costs (37,38). Therefore, the selection of the appropriate treatment regimen and DI according to the individual differences of patients reflects the concept of precision medicine.

The WJOG4407G trial in Japan compared two intravenous chemotherapy regimens, as shown in Table III. The first was mFOLFOX-6 combined with Bev and the second FOLFIRI combined with Bev (39). The preset dose of CPT-11 in the FOLFIRI/Bev protocol was 150 mg/m² according to the Japanese guidelines (40). The trial demonstrated that, with the increase of the number of treatment lines, the reduction trend of L-OHP was 85, 65 and 50 mg/m², whereas that of CPT-11 was 150, 120 and 100 mg/m². The median withdrawal time periods of L-OHP and CPT-11 were 5.1 and 8.5 months, respectively. L-OHP was withdrawn significantly earlier. The WJOG4407G trial indicated that the administration time of L-OHP was limited by the cumulative toxicity. The curative effects of the two regimens were approximate, while the prognostic trend of the FOLFIRI/Bev group was improved. This result was associated with a longer treatment duration, which was similar to the results of the MAVERICC trial, in which the dose used of CPT-11 was 180 mg/m² (41).

The DI changes of the second-line chemotherapy regimen were analyzed by the AXEPT trial and the Japanese FIRIS

trial (42,43). Most notably, the study subjects of the two trials were Asians. The AXEPT trial compared the CPT-11 and Cap (mXELIRI)/Bev and the FOLFIRI/Bev regimens and the FIRIS trial in Japan compared CPT-11 plus S-1 (IRIS) with the FOLFIRI regimen. According to the comparative analysis of the two trials, the ARDI of the second-line treatment (mXELIRI/Bev and IRIS regimens) was decreased to a higher extent compared with the other types of treatment. The ARDI of the FOLFIRI regimen for the second-line chemotherapy was decreased by ~10% and the ARDI of the mXELIRI/Bev and IRIS regimens remained at ~84.5%, as shown in Table IV. The DI of CPT-11 in the FOLFIRI regimen was higher than that noted in the mXELIRI/Bev and IRIS regimens. Nevertheless, in terms of efficacy and prognosis, mXELIRI/Bev and IRIS exhibited slightly improved performance. In addition, the incidence of adverse reactions was low. The two regimens balanced the efficacy and adverse reactions and exhibited the advantages of oral chemotherapeutic drugs. They were suitable for the second-line treatment of the mCRC population in Asia. The predecessor of mXELIRI is XELIRI regimen. The clinical application of the XELIRI regimen was limited due to severe diarrhea (44,45). Based on that, XELIRI was improved and modified in subsequent clinical trials to form mXELIRI, whereas the dose of CPT-11 was reduced from 250 to 200 mg/m² and that of Cap from 1,000 to 800 mg/m², which was approximately equal to the improvement of the FOLFOX regimen (43,46).

By analyzing the results of the clinical trials of the first and second-line two-drug regimens, it can be deduced that an optimal DI balance point can be achieved in the efficacy and incidence of adverse reactions, such as that noted by the ameliorated exploration of the mFOLFOX-6 regimen. The FOLFOX regimen is characterized by a transition process of FOLFOX from -1 to -7. The dose of L-OHP, the infusion mode and the dose of 5-FU were adjusted to balance the incidence of adverse reactions and the treatment efficacy. At present, the mFOLFOX-6 regimen is mainly recommended in the guidelines and has become widely accepted in clinical practice (18-21). The three first-line two-drug regimens are almost equivalent regarding their curative effects and they are frequently used as a back-line treatment or alternative treatment in the clinic. In addition, it is necessary to address the differences in the incidence of adverse reactions of the different regimens, the dose-limiting toxicity of L-OHP and the dosage form of chemotherapeutic drugs as well as their effect on the medical costs. The IRIS and mXELIRI regimens have been explored in the Asian patient population and have provided additional choices of second-line treatment regimens for patients with mCRC. Clinicians can select the optimal treatment regimen to balance the extent of the curative effects and the incidence of the adverse reactions in accordance with the specific situation of the patients. In order to ensure that the curative effect is not significantly reduced, the ARDI of the first-line treatment should be maintained at >90% and that of the second-line treatment at >80%.

4. DI of specific populations

Chemotherapy reduction and delay often occur in the elderly (>65 years) and frail patient population in the clinical

Table IV. Clinical trials of second-line two-drug regimens.

Clinical trial	Regimen	Average relative dose intensity, %	Dose intensity-related events, %	P-value	Overall survival, months	P-value	Progression-free survival, months	P-value	Other indicators, %	P-value	Grade 3 to 4 adverse events, %	P-value
AXEPT (42)	Irinotecan and capecitabine/Bev	85%	Incidence of delay, 80%; incidence of decrement, 55%	N/A	16.8	>0.05	8.4	>0.05	ORR, 24%	>0.05	Diarrhea, 7%; neutropenia, 17%	N/A
FIRIS (43)	FOLFIRI/Bev	74%	Incidence of delay, 91%; incidence of decrement, 75%	N/A	15.4	>0.05	7.2	>0.05	ORR, 18%	>0.05	Diarrhea, 3%; neutropenia, 43%	<0.05
	Irinotecan and S-1	84%	Incidence of delay/decrement, 93%	N/A	19.5	<0.05	5.8	<0.05	ORR, 19%	N/A	Neutropenia, 52%; diarrhea, 5%; anorexia, 5% Neutropenia, 36%; diarrhea, 21%; anorexia, 11%	<0.05

Bev, bevacizumab; ORR, objective response rate; FOLFIRI, 5-fluorouracil/folinic acid and irinotecan.

environment, which is closely interrelated to poor tolerance and recovery ability (47,48). It is important to note that limited data were available for the elderly and frail patients, which account for >50% of the advanced malignant tumor cases (49,50). The research on the DI of chemotherapy requires extensive exploration of the population under examination. The summary analysis of the TRIBE and TRIBE2 trials demonstrated that ORR and PFS were not associated with sex and age. However, additional analysis indicated that the incidence of adverse reactions in the elderly and female patients was higher (51). The trial proposed that, for patients with mCRC aged 70-75 years, the initial dose ought to be reduced and the pretreatment prior to chemotherapy should be performed when using the FOLFOXIRI/Bev regimen. The Korean Cancer Study Group conducted a multicenter trial on the reduction of the first cycle of first-line chemotherapy for elderly advanced malignant tumors and evaluated the incidence, chemotherapy compliance and efficacy of the reduction in the first cycle of chemotherapy (52). Among the 296 patients, the median age was 75 years (70-93 years). A total of 59.8% of the patients underwent treatment decrement. The average percentage of decrement in the whole patient population was 19.2% (4-47%) of the standard dose. In addition, the patients who received standard-dose chemotherapy in the first cycle were more likely to have it reduced in the second cycle. The trial demonstrated that the patients with reduced chemotherapy in the first cycle exhibited improved tolerance and chemotherapy compliance and lower incidence of adverse reactions compared with those who received the standard dose. It is important to note that non-significant differences were noted in OS and PFS between the two-dose regimens. The FOCUS2 trial conducted a clinical study on the decrement of the initial chemotherapy in elderly and frail patients with mCRC who were not suitable for standard-dose chemotherapy (53). A total of 459 patients with mCRC were included in the trial and received 80% of the standard chemotherapy dose as the starting dose. When the patients tolerated chemotherapy for six weeks, the dose was increased to reach the concentration levels of the standard dose. The median age of the patients was 74 years old (35-87 years old). A total of 68% of the patients were old and 71% of the patients were weak. It was deduced that the decrement of the initial dose of chemotherapy could result in an improved therapeutic effect, notably for elderly or frail patients. Furthermore, the trial recommended that the effect of combined chemotherapy was improved compared with that of the single drug. A clinical trial explored the efficacy and safety of FOLFIRI in the treatment of elderly and non-elderly patients with mCRC (54). It was found that the actual relative DI of CPT-11 and 5-FU was significantly higher in non-elderly patients than that noted in elderly patients ($P<0.001$). The relative DI of CPT-11 was $81\pm15\%$ (<70 years old), $75\pm15\%$ (70-74 years old) and $75\pm16\%$ (≥ 75 years old). The relative DI of 5-FU was $72\pm25\%$ (<70 years old), $67\pm26\%$ (70-74 years old) and $50\pm25\%$ (≥ 75 years old). Although the relative DI received by the elderly patients was comparatively low, the PFS and OS did not exhibit significant differences between the non-elderly and the elderly patients. A meta-analysis compared the FOLFIRI regimen with the 5-FU/folinic acid regimen in the first-line treatment of elderly and non-elderly patients with mCRC. The age limit was set to 70 years. The

summary analysis of 2,691 patients indicated that both elderly and non-elderly patients exhibited higher survival benefits in the combined chemotherapy regimen (55).

The hierarchical analysis of the HORG trial indicated that the OS of the patients with performance status (PS) 0-1 in the FOLFOXIRI group was 24 months. Notably, the OS of the patients with PS=2 was 6.6 months ($P=0.0001$). The same trend was observed in the FOLFIRI group. The OS of the patients in the FOLFIRI group with PS=0-1 was 20 months compared with 6.4 months ($P=0.03$) noted in patients with PS=2. This suggested the importance of the differences in the population functional status to disease prognosis and indicated that the PS score was an important factor affecting survival (22). The summary of nine clinical trials that examined patients with mCRC who were treated with first-line treatment demonstrated that the median PFS of the patients with PS=2 was 4.9 months, whereas the OS was estimated to be 8.5 months and the ORR 32%. The incidence of adverse reactions in the patients receiving standard-dose chemotherapy was higher (56). The updated subgroup analysis of the TRIBE2 trial indicated that the mCRC population with PS=0 exhibited higher benefit from the three-drug regimen with high DI ($P=0.05$) (57). It is suggested that the suitable population for the different DI of chemotherapy differs. High DI chemotherapy is suitable for patients with improved performance status evaluation and the PS score can be used as an excellent screening parameter.

More specifically, certain differences have been reported in the response of different populations to the DI of chemotherapy. It has been found that the American population has poor tolerance to 5-FU (58). Therefore, the recommended dose of 5-FU in the three-drug regimen according to the NCCN guidelines is $2,400\text{ mg/m}^2$, whereas that corresponding to the European and Chinese populations is $3,200\text{ mg/m}^2$. Moreover, several population differences have been reported in the tolerated dose of CPT-11. The recommended dose of CPT-11 according to the NCCN guidelines is 180 mg/m^2 , whereas the dose based on the Japanese guidelines is 150 mg/m^2 . A first-line dose exploration study of patients with mCRC based on different UDP glucuronosyltransferase family 1 member A (UGT1A) genotypes indicated that patients with different UGT1A genotypes should be treated with different doses of CPT-11. The maximum tolerated dose of patients with a genotype of $1^*/1$ was 450 mg/m^2 , whereas, for the $1^*/28$ and $28^*/28$ genotypes, these doses were 390 mg/m^2 and 150 mg/m^2 , respectively (59,60). The AXEPT trial applied the UGT1A genotype to guide the dosage of CPT-11 (42). In addition, individual differences in the patients' genetic predisposition and pharmacokinetic profile can lead to differences in the local drug dose or drug sensitivity of tumor cells (61). Neutropenia caused by chemotherapy can be used as an indicator of the efficiency of chemotherapy, which was also an important factor affecting survival (61). Although no significant differences were noted in the relative DI among patients without neutropenia, early-onset neutropenia and late-onset neutropenia, the local chemotherapeutic dose and treatment response were different. Neutropenia reflects the response rate and survival as an adverse reaction, which can improve the adjustment of the clinical dose (61).

Numerous clinical trials have suggested that the population containing elderly and frail patients was more prone to the

decline of chemotherapy DI (62). In summary, a certain degree of decline has a limited impact on the survival benefit. In contrast to these findings, it should be noted that the incidence of adverse reactions in this part of the population is relatively high. In specific populations, the combined regimen is also improved compared with the single-drug regimen, suggesting that it is feasible to increase the dose of chemotherapeutic drugs (53). In addition, the exploration of an optimal low-DI regimen in specific populations required further investigation. The elderly patient population and the patients with poor performance status present with different responses in drug efficacy and different incidence of adverse reactions (55,56). The survival benefit of the population with poor performance status is significantly low, which should be further distinguished. Furthermore, the difference in dose tolerance of CPT-11 in patients with different genotypes suggests that the markers related to chemotherapy efficacy and prognosis are worthy of further exploration (59). The differences in the pharmacokinetic parameters and in the genetic predisposition suggest that the local drug dose and sensitivity of tumor cells should be viewed from an accurate perspective. In addition, the occurrence time of neutropenia can be used as an alternative index to guide the adjustment of the chemotherapeutic dose (61).

5. Conclusion

Chemotherapy DI is a highly important factor to be considered for the balance of drug efficacy and adverse reactions. It can be used as a proxy measure of chemotherapy quality and prognosis (63). In the past decade, additional research has been conducted on the identification of novel drugs and regimens. The chemotherapy dose requires adjustment according to each patient and must not always follow the dosage recommended by the guidelines. The dose and frequency are adjusted mostly in radiotherapy research or in the treatment of certain rare malignant diseases (64). The pharmacokinetic study of drugs should not only be applied under specific experimental conditions since there are various complex parameters to be taken into consideration (65). The chemotherapy DI is affected by multiple factors, such as age, performance status, genotype, genetic predisposition, pharmacokinetics, a combination of chemotherapeutic drugs, the number of treatment lines, adverse reactions, liver and kidney function, complications and the psychological acceptance of patients (66-69). The development of precision medicine has led to the focus on individualized differences. The exploration related to refining the scheme has been carried out in different types of malignant tumors and therapeutic drugs (70,71). Cancer societies have initiated the establishment of consensus and guidelines on the dosage of drugs for specific patient populations, such as the elderly, obese and overweight patients (72,73). This disagrees with our conventional thinking, which involves the use of the body surface area and the bodyweight to calculate the dose of chemotherapy while ignoring the discrepancies noted in the response of different populations to treatment.

The clinical trials of the three-drug and two-drug regimens reflected the changes in the chemotherapy DI of the clinical trial environment. In clinical treatment, the baseline condition

of the patient population is more complex and the implementation of the treatment regimen and clinical benefits vary greatly among individuals. This suggests that clinicians should reasonably arrange the chemotherapy regimen according to each individual, including regimen and dose, time arrangement, administration mode and combined administration. It was found that the survival benefit of the treatment mode of the combined administration (increasing chemotherapeutic drugs or combined targeted drugs) was outstanding, whereas the incidence of adverse reactions was increased. The elderly and frail patient population is more prone to the development of adverse reactions and exhibits higher therapeutic utility in low-dose intensive chemotherapy (74). The exploration of the optimal treatment scheme and DI for different populations requires substantial research in order to maximize the effectiveness of clinical treatment. At present, certain studies focus on optimizing the physical and chemical properties of drugs and increasing the response of patients to anticancer drugs by increasing the local concentration following drug absorption (75,76). In addition, the reduction of adverse reactions and the improvement of the performance status can increase the DI of chemotherapy and improve the curative effect (77,78). As a regulator of CPT-11 in patients with mCRC, Huangqin Decoction can reduce gastrointestinal toxicity and reduce the events of chemotherapy reduction caused by toxicity (79). Therefore, it is worth assessing the effective adjuvant treatment methods or complementary alternative medicine, such as Traditional Chinese Medicine, to reduce adverse reactions and improve performance status.

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Authors' contributions

XC and PX performed data analysis and manuscript writing. SZ conceived and reviewed the paper for intellectual content. All authors read and approved the final manuscript. Data sharing is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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